Journal of the American College of Cardiology Vol. 58, No. 16, 2011

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.05.058

YEAR IN CARDIOLOGY SERIES

The Year in Clinical Cardiac Electrophysiology

Gregory M. Marcus, MD, MAS,* Melvin M. Scheinman, MD,* Edmund Keung, MD†

San Francisco, California

Atrial Fibrillation

Several important studies related to the treatment of atrial fibrillation (AF) were published in the past year. In addition, building on recent data, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the Heart Rhythm Society (HRS) provided updates to the AF guidelines.

Van Gelder et al. (1) published the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) trial, the first formal assessment of alternative rate control goals in AF. Six hundred and fourteen patients in the Netherlands were enrolled in this prospective, multicenter, randomized, open-label, noninferiority trial and randomly assigned to a "lenient rate-control" strategy (target resting heart rate <110 beats/min) versus a "strict rate-control" strategy (target resting heart rate <80 beats/min and a target heart rate <110 beats/min during moderate exercise). Rate control was achieved during a dose-adjustment phase by the use of 1 or more negative dromotropic drugs, including beta-blockers, nondihydropyridine calcium-channel blockers, and digoxin, at various doses. The primary endpoint was a composite of death from cardiovascular causes, hospitalization for heart failure (HF), stroke, systemic embolism, major bleeding, arrhythmic events including syncope, sustained ventricular tachycardia (VT), cardiac arrest, life-threatening adverse effects of rate control drugs, and insertion of a pacemaker and implantable cardioverter-defibrillator (ICD). To test the hypothesis that a lenient rate-control strategy would be noninferior to strict rate control, the power of the study was based on the ability to exclude an absolute increase in 10 percentage points in the rate of the primary outcome at 2.5 years in the lenient-control group. At enrollment, participants had to have permanent AF for up to 12 months, with a mean resting heart rate >80 beats/min, and receiving anticoagulant therapy dictated by thromboembolic risk factors. Important exclusion criteria included New York Heart Association (NYHA) functional class IV HF, HF necessitating hospital admission, or cardiac surgery within the previous 3 months (2).

The baseline characteristics of the patients were generally well balanced, with the exception of more coronary artery disease, statin use, and higher diastolic blood pressure in the lenient-control group. The mean resting heart rate was 93 ± 9 beats/min in the lenient-control group compared to 76 ± 12 beats/min in the strict-control group ($p < 0.001$). A total of 81 patients (38 in the lenient-control group and 43 in the strict-control group) reached the primary outcome. The 3-year estimated cumulative incidence of the primary outcome was 12.9% in the lenient-control group and 14.9% in the strict-control group, resulting in an absolute difference between lenient control and strict control of −2 percentage points (90% confidence interval [CI]: −7.6 to 3.5 percentage points). The criteria for noninferiority in the lenient-control group was achieved with a p value <0.001. These results did not meaningfully change after adjustment for covariates that were not well balanced between the groups. In addition, no differences in the reports of various AF-related symptoms were observed. Finally, fewer visits were required to achieve the target heart rate in the lenient-control group (median of 0 compared to median of 2 for the strict-control group).

This study suggests that a lenient rate-control approach targeting resting heart rates <110 beats/min may be reasonable and more easily achieved in AF patients compared to the conventionally recommended target of <80 beats/min. Several caveats should be considered before applying this broadly to clinical practice. First, as patients with a recent HF hospitalization were excluded, these results may not apply to such patients. Second, the adverse effects of prolonged faster ventricular rates may require several years, and follow-up was terminated in this study after a maximum of 3 years. In fact, as the primary outcome was specifically time to first occurrence of the composite outcome (meaning participants were censored after that first outcome), the cumulative effects of these strategies for patients who experienced 1 of the many adverse events that comprised that composite outcome is not known. Third, whereas 98% of patients in the lenient-group achieved the target heart rate, only 67% in the strict-control group achieved their target heart rate—this may have reduced the power to detect an advantage (or disadvantage) of the "on treatment" out-

From the *Department of Cardiac Electrophysiology, University of California San Francisco, San Francisco, California; and the †Veterans Affairs Medical Center, San Francisco, California. Dr. Marcus has received speaker's fees from Medtronic and St. Jude Medical; is a consultant for InCarda; and has received research support from St. Jude Medical, Sanofi-Aventis, and Astellas. Dr. Scheinman has received speaker's fees from Biotronik, St. Jude Medical, Boston Scientific, and Medtronic. Dr. Keung has reported that he has no relationships relevant to the contents of this paper to disclose.

Manuscript received April 27, 2011; accepted May 5, 2011.

comes. Perhaps most importantly, it must be remembered that "lenient" still required a heart rate <110 beats/min.

Given promising, but conflicting, data regarding the efficacy of omega-3 fatty acid supplementation for the prevention of AF recurrence, Kowey et al. (3) randomly allocated 663 AF patients stratified by a baseline diagnosis of paroxysmal AF or persistent AF in a ratio of 5:1 to 4 g a day of prescription omega-3 or placebo in a double-blind, multicenter trial. Patients with persistent AF had to have been successfully pharmacologically or electrically cardioverted, and the presence of sinus rhythm at study entry was required for all participants. Each 1 g of the prescription omega-3 included approximately 465 mg of eicosapentaenoic acid and 375 mg of docosahexaenoic acid. Patients receiving antiarrhythmic drugs, patients taking omega-3 fatty acids within 30 days of enrollment, and patients with specific structural heart disease were excluded. Five hundred and eighty-four participants (88% of those enrolled) completed the 6-month study. The baseline characteristics and proportions with paroxysmal and persistent AF were generally well balanced between the treatment groups. No statistical difference was noted in the primary endpoint of first symptomatic recurrence of AF or atrial flutter: in patients with paroxysmal AF, there were 129 events (48%) in the placebo group and 135 (52%) in the prescription group (hazard ratio [HR]: 1.15, 95% CI: 0.90 to 1.46, $p = 0.26$). In patients with persistent AF, 33% of the placebo group and 50% of the prescription drug group achieved this primary endpoint (HR: 1.64, 95% CI: 0.92 to 2.92). Of note, these outcomes were examined in multiple ways (including with and without a pre-specified intention to treat analysis and including analyses within multiple subgroups), without any detection of benefit in the prescription arm.

Interestingly, patients receiving the prescription omega-3 fatty acid exhibited a statistically significantly lower average heart rate during the first occurrence of symptomatic AF or atrial flutter compared to patients on placebo, with a mean difference of −6.99 beats/min (95% CI: −13.12 to −0.64 beats/min, $p = 0.03$).

Although this study suggests there is no benefit of omega-3 fatty acid prescription to prevent recurrent AF, there are several limitations that should be considered. First, follow-up was limited to 6 months. This likely provides ample evidence that an acute and efficacious electrophysiologic effect is not present, but chronic anti-inflammatory or antifibrotic effects that might reduce the risk of AF over longer follow-up may still be present. In addition, the primary endpoint involved only symptomatic episodes, and potential differences in the true underlying AF burden (and long-term sequelae of AF such as stroke) between groups remain unknown. However, that ventricular rates during atrial arrhythmia episodes were slower in the prescription group may suggest that the chances of asymptomatic episodes would be higher in that group. Although the study was powered based on event rate estimates that were higher than those actually observed (potentially resulting in a type II error or false negative results), the point estimates generally favored placebo, making such a type II error in favor of the prescription unlikely. Finally, as acknowledged by the authors, this study does not exclude the possibility of benefit in other more specific AF populations, such as patients with severe heart disease or patients in the post-operative setting.

Several important studies involving new ways to think about and prevent stroke in AF were published in the last year. First, a large trial of a factor Xa inhibitor in AF was published. Connolly et al. (4) published the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial, in which 5,599 AF patients with at least 1 additional risk factor for stroke not receiving vitamin K antagonist therapy (either because it had already been demonstrated to be unsuitable or because it was expected to be unsuitable) were randomly assigned to the direct factor Xa inhibitor, apixaban, 5 mg twice daily, or aspirin at a dose of 81 to 324 mg daily. A reduced dose of apixaban of 2.5 mg twice daily was used for participants who were older than 80 years of age, had a body weight of 60 kg or less, or a serum creatinine of 1.5 mg/dl or higher. The primary efficacy outcome was the occurrence of stroke or systemic embolism, and the primary safety outcome was the occurrence of major bleeding.

The baseline characteristics were well balanced between treatment groups. Two thousand sixteen (40%) participants had previously received and discontinued a vitamin K antagonist. In 43% of cases, the physician had determined that international normalized ratio (INR) measurements could not be or were unlikely to be maintained, and vitamin K antagonist therapy was considered unsuitable in 21% because the risk of stroke was only moderate (a $CHADS_2$ score of 1). In 15%, the only reason vitamin K antagonists were unsuitable was because the patient did not want to take them. The study was terminated early with a mean follow-up duration of 1.1 years for an interim analysis that met the pre-specified stopping rule for efficacy in favor of apixaban. There were 51 primary outcome events (1.6% per year) in the apixaban group and 113 (3.7% per year) in the aspirin group (HR with apixaban: 0.45, 95% CI: 0.32 to 0.62, $p < 0.001$). There were 44 major bleeding events (1.4% per year) in the apixaban group and 39 (1.2% per year) in the aspirin group (HR with apixaban: 1.13, 95% CI: 0.74 to 1.75, $p = 0.57$). While no significant differences in hemorrhagic stroke were observed, more minor bleeding with apixaban occurred with borderline statistical significance (HR: 1.24, 95% CI: 1.00 to 1.53, $p = 0.05$). The risk of permanent discontinuation was 12% lower in the apixaban group (HR: 0.88, 95% CI: 0.78 to 0.99). Serial liver function tests revealed no differences between the groups. In multiple subgroup analyses, the superior efficacy of apixaban with similar adverse events was generally consistent.

It appears that, in AF patients with at least 1 additional risk factor for stroke that are deemed unsuitable for vitamin K antagonist therapy, treatment with apixaban compared to

aspirin reduces the risk of stroke without significantly increasing the risk of bleeding. It is important to understand that the study was stopped early for efficacy. Although that may reflect true efficacy that surpassed the initial power estimates, chance may have played a role. However, the study was stopped only after meeting very stringent stopping rules that had been pre-specified. Conversely, the shorter study period may have been insufficient to detect a cumulative risk of bleeding or other adverse events with this new drug. In addition, while these findings will likely be applicable to a substantial number of AF patients currently prescribed aspirin, future studies comparing the drug to warfarin or the newer direct thrombin inhibitors are necessary to inform us regarding the broader application of this therapy.

Theoretically, a successful AF ablation might reduce the long-term risk of stroke. However, an important study published this year suggests that the procedure itself may substantially increase the risk for asymptomatic cerebral thromboembolism (5). Gaita et al. (5) performed magnetic resonance imaging (MRI) of the brains of 234 consecutive AF patients from 3 centers 1 day before and 1 day after AF ablation. The $CHADS_2$ score was 0 in 46% and 1 in 43%. The ablation procedures were generally standard. In all patients, a transesophageal echocardiogram was used to exclude left atrial thrombus before proceeding with the procedure. A control group of 65 patients undergoing cardioversion, all with standard precautions for stroke prophylaxis, also underwent the same serial brain MRI studies. None of the cardioversion patients exhibited either a clinical stroke or evidence of new ischemic cerebral lesions by MRI. One AF ablation patient experienced a transient ischemic attack (0.4%, a number compatible with and even lower than previous reports [6]). However, asymptomatic new ischemic lesions were noted in the brains of 33 (14%) patients: 25 were cortical, 7 were in the cerebellum, and 1 was in the basal ganglia. In all 33, a neurologic examination was negative, and carotid Doppler studies showed no significant abnormalities. Independent risk factors for these asymptomatic ischemic lesions included cardioversion during the procedure and an activated clotting time (ACT) value $<$250 s. Mechanisms of intraprocedural thromboembolism might be related to char formation at the site of radiofrequency delivery, thrombus formation on catheters or sheaths, air embolism, or thrombus formation immediately after cardioversion (7,8). It important to note that, although the goal ACT between 250 and 300 s was in accordance with the Venice International Consensus on AF ablation (9), the HRS guidelines, citing previous studies demonstrating the risk of in situ thrombosis adherent to transseptal sheaths, recommend maintaining ACTs between 300 and 350 s (10). Cardioversion may have posed higher risks because the resultant atrial stunning compounded the prothrombotic effects of ablation or perhaps because more ablation lesions were delivered to the more persistent AF patients that ultimately required cardioversion. Although the neurologic examinations were normal, those lesions may result in more subtle but still clinically meaningful long-term consequences, particularly in these patients who are likely at risk for recurrent cerebral events.

At the end of an AF ablation case, there is typically a gap in anticoagulation therapy between sheath removal and enoxaparin or heparin administration to reduce the risk of catheter access site bleeding, potentially increasing the risks for periprocedural thromboembolism as described in the preceding text. Therefore, it is worth noting an interesting report from Di Biase et al. (11) published in the last year, describing the outcomes of 2,618 AF ablation patients in whom the ablation was performed on therapeutic warfarin (INR $>$2). Compared to patients bridged with enoxaparin, patients maintained on warfarin exhibited significantly fewer periprocedural strokes or transient ischemic attacks: 27 (1.1%, 95% CI: 0.72% to 1.58%) of 2,488 undergoing ablation with an 8-mm catheter after warfarin was discontinued; 12 (0.9%, 95% CI: 0.46% to 1.56%) of 1,348 undergoing ablation with a 3.5-mm open-irrigated catheter after warfarin was discontinued; and 0 of 2,618 undergoing ablation with a 3.5 mm open-irrigated catheter while on therapeutic warfarin ($p < 0.05$). There were no differences in major bleeding or frequency of pericardial effusion. However, pericardial effusion patients on therapeutic warfarin more often required fresh frozen plasma ($p < 0.001$), required a median larger number of blood units for transfusions ($p = 0.043$), and had a larger volume of pericardial aspiration ($p < 0.001$) than did pericardial effusion patients in whom warfarin had been discontinued. Although this was a nonrandomized prospective observational study, the on-warfarin patients had a higher prevalence of nonparoxysmal AF and more often had a $CHADS_2$ score $\geq$2. Although the relative timing of performing these procedures is not described in the paper, one potential caveat is that, if in fact the majority of on-warfarin procedures were performed later, it is possible that the operators and institutions were more experienced performing the procedures during a greater proportion of the on-warfarin cases versus the off-warfarin cases. Regardless, consistent with some of the practices in many electrophysiology groups that are becoming more common, performing these cases on therapeutic warfarin appears to be a reasonable approach.

Two important studies reported long-term follow-up results of AF ablation this past year. Interpretation of the results is complex, given frequent repeat ablation procedures, variable patient characteristics, and variable types of recurrences (macro–re-entrant atrial tachycardias versus AF). In brief, Ouyang et al. (12) described 161 consecutive paroxysmal AF patients with normal left ventricular (LV) function undergoing AF ablation in Germany, finding that stable sinus rhythm was present in 75 (47%) patients after the first procedure with a median 4.8 years (range 0.33 to 5.5 years) of follow-up. However, after a median of 1 (range 1 to 3) procedures, stable sinus rhythm was achieved in 128 patients (80%) during a median follow-up of 4.6 years

(range 0.33 to 5.5 years). Nineteen (15%) of those sinus rhythm patients continued to take antiarrhythmic drugs. Weerasooriya et al. (13) reported the long-term results of 100 paroxysmal and persistent AF patients undergoing ablation in Bordeaux, France. After a single ablation procedure, actuarial arrhythmia-free survival rates were 40 ± 5%, 37 ± 5%, and 29 ± 5% at 1, 2, and 5 years, respectively. By a median of 5 years, 51% had undergone at least 1 repeat ablation procedure. The actuarial survival rates after the last ablation procedure were 87 ± 4%, 81 ± 4%, and 63 ± 5% at 1, 2, and 5 years, respectively. In both studies, recurrences were most common in the first 6 months. Also, in both, there was evidence of a steady rate of recurrence. These studies suggest that AF ablation patients should be counseled regarding the possibility of long-term recurrence and the potential need for repeat procedures. Perhaps most importantly, in accordance with current guidelines (10), these studies show that AF ablation should not be considered an alternative to anticoagulation therapy for long-term stroke prevention, particularly in patients at high risk for stroke.

AF Guideline Updates

Several updates to the ACCF/AHA/HRS AF guidelines were published this past year. Based on the RACE II trial described in the preceding text (1), there is a new recommendation for rate control during AF: designated as a Class III recommendation, the 2011 ACCF/AHA/HRS AF guidelines state that there is no benefit of treatment to achieve strict versus lenient rate control as defined in the preceding text (14). The guidelines restrict this recommendation to patients with stable ventricular function (defined as an ejection fraction >40%) and no or acceptable symptoms related to the arrhythmia. They also mention within this recommendation that uncontrolled tachycardia over time may be associated with a reversible decline in ventricular performance. In large part due to evidence provided by the ACTIVE-A (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) trial (15), a study reviewed in detail in last year's Year in Clinical Cardiac Electrophysiology (16), there is now a Class IIb recommendation that clopidogrel may be added to aspirin to reduce the risk of major vascular events, including stroke, in AF patients for whom oral anticoagulation therapy with warfarin is considered unsuitable due to patient preference or the physician's assessment of the patient's ability to safely sustain anticoagulation therapy (Level of Evidence: B) (14). Based largely on findings from the ATHENA (A Placebo-Controlled, Double-Blind, Parallel-Arm Trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter) trial (17), there is a new Class IIa recommendation that dronedarone is reasonable to decrease the need for cardiovascular-related hospitalizations in paroxysmal AF patients or after cardioversion of persistent AF (Level of Evidence: B) (14). And, on the basis of the ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease) trial (18), a Class III-Harm recommendation, dronedarone should not be administered to patients with class IV heart failure or patients with an episode of decompensated heart failure in the past 4 weeks, especially in the setting of an LV ejection fraction ≤35% (Level of Evidence: B) (14). In the revised "Maintenance of Sinus Rhythm" flow chart, dronedarone is now included along with flecainide, propafenone, and sotalol as a first-line antiarrhythmic drug choice for AF patients with no or minimal heart disease (whether hypertension is present or not) and along with dofetilide and sotalol for patients with coronary artery disease (14).

On the basis of growing evidence from multiple studies, several recommendations regarding catheter AF ablation were refined in the updated guidelines. Although previously a Class IIa recommendation with Level of Evidence: C, catheter ablation performed in experienced centers is now a Class I recommendation (Level of Evidence: A) as a means to maintain sinus rhythm in significantly symptomatic, paroxysmal AF patients who have failed an antiarrhythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease (14). As a Class IIa recommendation, catheter ablation is now considered reasonable to treat symptomatic persistent AF (Level of Evidence: A). And, as a Class IIb recommendation, it is reasonable to use catheter ablation in the treatment of symptomatic paroxysmal AF patients with significant left atrial dilation with or without significant LV dysfunction (Level of Evidence: A) (14).

Finally, in a separate focused ACCF/AHA/HRS guideline update dedicated to dabigatran in AF and based primarily on the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study (19) (reviewed in detail in last year's Year in Clinical Cardiac Electrophysiology) (16), dabigatran now has a Class I recommendation as a useful alternative to warfarin for the prevention of stroke and systemic embolism in patients with AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure, or advanced liver disease (Level of Evidence: B) (20).

Ventricular Arrhythmias

Weisfeldt et al. (21) performed a large epidemiologic study investigating the underlying ventricular rhythms in patients with cardiac arrest at home versus in a public setting. While automated external defibrillators (AEDs) have been shown to improve survival after out-of-hospital cardiac arrest in public settings (22) (such as airports [23] and casinos [24]), layperson use of AEDs in residential settings has not proved to be of benefit (25), potentially because of a relatively low prevalence of arrests due to ventricular fibrillation (VF) or

pulseless VT. In fact, recent data suggest that the incidence of these "shockable rhythms" (VF and pulseless VT) may be decreasing in general (26,27).

This was a prospective population-based cohort study utilizing the Epidemiologic Cardiac Arrest Registry of the Resuscitation Outcomes Consortium at 7 U.S. sites and 3 Canadian sites. From December 2005 to April 2007, complete data were available on 14,509 nontraumatic cardiac arrest patients for whom external defibrillation was attempted by either lay bystanders or emergency medical services (EMS) or who were treated with chest compressions by EMS alone. The initial cardiac-arrest rhythm was known for 12,930 patients (92%). To compare arrests that occurred at home versus public settings, the primary analyses excluded the 1,324 patients with an arrest in a residential institution (such as a nursing home) or other private (not home) locations. The median time from the 911 call to EMS arrival was 5.0 min (interquartile range [IQR]: 3.6 to 6.6 min) for arrests in public and 5.6 min (IQR: 4.3 to 7.1 min) for arrests at home. The initial ascertainable rhythm was VF or pulseless VT (and, in rare cases, a hypotensive supraventricular tachycardia) in 3,336 of the 12,930 arrests (26%). Of the 3,451 patients with arrests at home, 1,193 (35%) had VF or pulseless VT compared with 600 of 1,003 (60%) with an arrest in a public location. After adjusting for age, sex, bystander-administered CPR, and time from 911 call to the arrival of EMS, there was a 2.28 greater odds of initial VF or pulseless VT in a public location versus at home (95% CI: 1.96 to 2.66 greater odds, $p < 0.001$). After restricting the analysis to bystander-applied AEDs, 25 of 69 (36%) patients with arrests in the home compared to 125 of 159 (79%) patients with arrests in public were found to have a shockable rhythm (after multivariable adjustment, there was a 4.48 greater odds of a shockable rhythm in patients with an arrest in public, 95% CI: 2.23 to 8.97 greater odds, $p < 0.001$). Survival was generally better for patients with cardiac arrests in public compared to those with arrests at home. These findings may help explain the disparate findings regarding success in saving lives with AEDs in public versus no proven substantial benefit of these devices when used in private homes. The exact reasons why less VF/pulseless is observed as the initial rhythm at home remain unknown. The researchers suggest that patients who arrest at home are typically older and more likely to have chronic diseases that limit activities outside the home. The reported timing from initial arrest to arrival of EMS personnel was provided by bystanders and may not have reflected the true time—for example, it is not clear how the timing of a "witnessed" event in a patient who had been sleeping would have been counted, whereas presumably all or most of the public arrests may have resulted in a more dramatic and obvious collapse more amenable to a rapid 911 call. The authors conclude that, given the relatively low incidence of shockable arrhythmias in the home cardiac arrests, treatment strategies at home emphasizing prompt and high quality bystander-delivered CPR may be as effective as the widespread deployment of AEDs in homes.

A second important study on ventricular arrhythmias and sudden death published this past year sought to understand the apparent paradox regarding the poor performance of primary prevention ICDs in preventing death within the first month after a myocardial infarction (MI). Although sudden (presumed arrhythmic) death remains an important cause of death after MI, with the highest risk occurring shortly after the MI, randomized trials assessing ICD implant within the first month after MI have failed to show any mortality benefit (28,29). Pouler et al. (30) studied all of the available autopsy reports of deceased patients that participated in VALIANT (Valsartan in Acute Myocardial Infarction Trial) (30). The VALIANT trial randomly allocated 14,703 patients with clinical evidence of heart failure or LV dysfunction (ejection fraction <35% by echocardiography or ventriculography, or ejection fraction <40% by radionuclide imaging), or both, after an acute MI to valsartan, captopril, or both. There were 2,878 deaths over a median follow-up of 24.7 months. At the discretion of treating physicians and according to local practices, an autopsy was performed in 444 (15%) of the deaths, and reports were available for 398 patients. Compared to patients who died without an autopsy, patients who underwent an autopsy were younger, more often white, had higher diastolic blood pressures, and were more likely to have a history of hypertension; and they were less likely to have diabetes mellitus, dyslipidemia, or to have undergone a primary percutaneous angioplasty. The majority of patients with autopsies performed (65%) were in Russia, where mandated autopsies were more common. By clinical information only, 105 (26%) were classified as dying suddenly and unexpectedly. Of these 105, 54 (51%) had no specific autopsy evidence of cause of death other than the index MI and were, therefore, presumed to have died of a ventricular arrhythmia. Six (6%) died within 1 week of the MI: 3 had myocardial rupture and 3 were only found to have evidence of the index MI (death attributed to arrhythmia). Twenty-eight (27%) of the 105 patients had specific evidence of recurrent MI, 10 (10%) had cardiac rupture, 4 (4%) had evidence of overwhelming pulmonary congestion, 2 (2%) had evidence of stroke or pulmonary embolism, and 1 (1%) had evidence of a drug overdose. The autopsy records resulted in the reclassification of the cause of death in 69 (17%) of the 398 patients, mostly because of previously unrecognized fatal MI or myocardial rupture in patients who died suddenly. Importantly, the percentage of sudden deaths due to recurrent MI or myocardial rupture was highest in the first month and then declined substantially over time. In contrast, the percentage of likely true arrhythmic deaths increased significantly over time. Specifically, within the first month, only 20% of sudden deaths were presumed due to arrhythmia, whereas 75% of all sudden deaths after 3 months were assumed to be arrhythmic ($p < 0.0001$). These data are compatible with and may in fact

explain previous studies that were unable to demonstrate a mortality benefit of ICDs early after MI (28,29), and further supports the current guideline to wait at least 40 days after an MI before implanting an ICD (31).

Cardiac Resynchronization Therapy

The RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial) study reconfirmed that the addition of cardiac resynchronization therapy (CRT) to an ICD provided additional benefits for mild-to-moderate HF patients (32). In this multicenter clinical trial, 1,798 NYHA functional class II and III patients with LVEF ≤30% and QRS duration ≥120 ms on optimal medical therapy were randomly assigned to receive either an ICD or cardiac resynchronization therapy with defibrillator (CRT-D). Approximately one-third of the patients had nonischemic cardiomyopathy and 71% to 73% had left bundle branch block (LBBB). The mean QRS duration was 157 ms. The primary endpoint was death from any cause or hospitalization for HF. During a mean follow-up period of 40 months, there were significantly more patients in the ICD group reaching the primary endpoint than in the CRT-D group (40.3% vs. 33.2%; HR: 0.75). However, device-related complications occurred twice as often in the CRT-D group, most commonly due to LV lead dislodgement and infection. In contrast to findings from the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) study, CRT-D resulted in additional mortality benefit when compared to the ICD alone.

Several subsequent reports from the MADIT-CRT trial greatly advanced our understanding of CRT in HF (33). In a subgroup analysis of MADIT-CRT patients (NYHA functional class I or II and LVEF ≤30%, QRS ≥130 ms), when compared with ICD-only therapy, CRT-D provided significantly more benefits (reduction in HF event or death, LV volume, and risk of ventricular tachyarrhythmias, and improvement in LVEF) only in patients with LBBB (34). It was suggested that more generalized dyssynchrony was present with LBBB because of abnormal activation of the interventricular septum and markedly delayed activation of the lateral LV. Consequently, more reverse remodeling from better resynchronization led to better clinical outcome in LBBB patients. This finding prompted the Circulatory System Devices Panel of the U.S. Food and Drug Administration to recommend approval of CRT-D therapy to patients who met the MADIT-CRT study enrollment criteria with an added requirement that these patients also have LBBB. The improvement in clinical outcomes from CRT-D was found to link directly to reverse remodeling from resynchronization pacing (35). The CRT significantly reduced cardiac size (left ventricular end-diastolic volume [LVEDV] and left ventricular end-systolic volume [LVESV] indexes) and improved performance (LVEF). A 10% decrease in LVEDV was associated with a 40% risk reduction. Sex was also a factor in clinical outcomes: women in the MADIT-CRT trial benefited more from CRT, with greater reductions in death or heart failure, all-cause mortality, and greater improvement in reverse modeling (36).

The significance of bundle branch block morphology and other predictors of CRT outcomes were further examined in a retrospective analysis of data collected during 2005 and 2006 from the Medicare Implantable Cardioverter-Defibrillator Registry (37). The 14,946 patients with CRT-D had 1- and 3-year mortality rates of 12% and 32%, respectively. After age ≥80 years and NYHA functional class IV status, RBBB and ischemic cardiomyopathy were the next strongest predictor of mortality: death was twice as high as in patients with LBBB and nonischemic cardiomyopathy together. The role of HF etiology in NYHA functional class I and II patients treated with CRT was analyzed using data from the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction Study) trial (38). The CRT significantly reduced the percentage of patients with the worsening HF composite response in 277 nonischemic patients, but not in 333 ischemic patients. Reverse remodeling, as indicated by the LVESV index, was greater in the nonischemic cardiomyopathy patients. However, the latter group was more often younger, female, had a LBBB and a longer QRS duration, received beta-blockers, and exhibited several other factors known to have favorable influence on CRT. Not surprisingly, multivariable analysis showed that HF etiology was not an independent predictor of a favorable response to CRT. On the other hand, in a single-center study involving 503 patients, CRT resulted in greater reverse remodeling (LVEF and LVEDV) and better 4-year survival for nonischemic cardiomyopathy (77%) than ischemic cardiomyopathy (44%) (39).

The question of what constitutes a CRT responder was raised by a study in which 17 different primary response criteria were identified from 26 relevant articles (40). Agreement between different methods to define CRT responder was found to be poor 75% of the time and strong only 4% of the time. Nevertheless, taking all the published studies together, the most likely suspect list for adverse clinical predictors in CRT consists of advanced age, male sex, ischemic cardiomyopathy, NYHA functional class IV symptoms, non-LBBB, QRS <150 ms, significant LV scarring, and severe noncardiac comorbidities such as pulmonary disease, pulmonary hypertension, renal dysfunction, and diabetes mellitus (41).

In addition to the preceding factors, LV pacing site is a major determinant in successful CRT. The current consensus is to position the LV lead in a lateral or posterolateral branch of the coronary sinus. The MADIT-CRT study data were analyzed for the effect of LV lead position on clinical outcomes (42). The benefit was similar for leads in the anterior, lateral, or posterior position. However, apical lead location when compared to nonapical position was associated with a significantly higher risk for the composite

primary endpoint of heart failure/death (HR: 1.72) and for death alone (HR: 2.91). Apical LV pacing was associated with a significantly worse clinical outcome in LBBB and nonischemic cardiomyopathy. The degree of reverse remodeling from CRT was similar among all pacing sites, but a trend toward less reverse remodeling was seen in apical LV pacing. Interestingly, apical pacing was associated with a worse outcome only in men, not in women. The most important message of the study was that LV apical lead placement should be avoided as much as possible because of its detrimental effect. However, it is important to note that, while the primary endpoint occurred more frequently with apical pacing (22%) compared to nonapical pacing (13%), it was lower than that observed in the ICD group (25.3%) (33). Therefore, although patients with an existing apical LV lead may not reap the maximal benefit from CRT, there is no evidence from this study that it actively worsens the clinical outcomes compared to patients treated with an ICD alone.

Implantable Cardioverter-Defibrillators

The long-term mortality benefit of ICDs in primary prevention was investigated in the MADIT-II study (43). In the initial median follow-up of 1.5 years, treatment with an ICD reduced total mortality by 31%. This benefit was sustained at 8 years of follow-up (34%). At 8 years, the cumulative probability of total mortality remained significantly lower among ICD patients (49%) than non-ICD patients (62%). Compared to the first 3.5 years of follow-up, at the end of 8 years, the average survival gain increased from 0.167 to 0.52 years and the number of ICD patients needed to save 1 life decreased from 17 to 8. The analysis also confirmed that right ventricular (RV) pacing in dual-chamber ICD recipients in MADIT-II study patients adversely affects long-term mortality. Whereas no significant difference in mortality rate was detected between ICD patients with low (<50% pacing) and high (>50%) RV pacing during the first 3 years, the increased mortality in the high RV pacing group from 3 to 8 years of follow-up negated any apparent survival benefit of the ICD over that period (44). Of significant interest is that the adverse effect of high RV pacing was not found in the presence of LBBB. Among non-LBBB patients, only low RV pacing was associated with a significant reduction in mortality during the 8-year follow-up period. A provocative corollary is that RV pacing may not be harmful to patients with systolic dysfunction and LBBB, as the incremental dyssynchrony induced by RV pacing is likely much less significant.

ICD therapy is a Class IIb indication for patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) (45). A retrospective study involving 106 patients with ARVC who received an ICD because of 1 or more arrhythmia risk factors that included syncope, nonsustained VT, familial sudden death, and sustained ventricular tachyarrhythmias induced with electrophysiology testing was performed to better identify patients who would benefit from ICD therapy. Syncope significantly predicted lifesaving ICD intervention, and a history of nonsustained VT (≥3 consecutive ventricular complexes with a rate of >100 beats/min, lasting <30 s recorded on 24-h Holter monitoring or during exercise testing) signified intermediate risks. Ventricular tachyarrhythmia inducibility had poor positive and negative predictive values for ICD intervention, 35% and 74%, respectively. None of the 27 asymptomatic patients with isolated familial sudden death had appropriate ICD therapy. Inappropriate ICD therapy occurred in 19%, and a device-related complication was observed in 17% of the patients. The results of this study strongly support prophylactic insertion of an ICD in AVRC patients with syncope and serious consideration for patients with asymptomatic, spontaneous nonsustained VT. The study suggests that primary prevention ICDs may not be indicated in asymptomatic ARVC patients with isolated familial sudden death.

The DINAMIT (Defibrillation in Acute Myocardial Infarction Trial) showed that implantation of ICDs within 6 to 40 days of MI reduced arrhythmic death but not mortality among patients with low LVEF (≤35%) and low heart rate variability (28). The reduction of arrhythmic deaths (67%) was more than offset by an increase in nonarrhythmic deaths (70% relative risks when compared to non-ICD group). As in the preceding text, a recent autopsy study has taught us more about the likely mechanisms of death in this kind of patient population (30), and a recent re-examination of the DINAMIT study data explored whether the ICDs themselves may have resulted in some harm (46). The most striking finding was that, after patients received appropriate ICD therapy (70% shock), there was a more than twofold increase in all-cause mortality (36%) compared with either the control group (16%) or the ICD group with no appropriate therapy (13%). Shocks are known to be associated with higher mortality in the MADIT-II and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) patients. Patients with appropriate shocks in the DINAMIT study also had more coexisting cardiac events (MI and HF) than patients enrolled in the other 2 trials. Ventricular tachyarrhythmias requiring shocks (30% VF), especially during the first year after MI (68% occurrence), may simply be a marker of more severe underlying cardiac disease and a poorer prognosis. Only 26% of the studied patients had in-hospital percutaneous transluminal coronary angioplasty for MI, and the percentage receiving stents were likely to be even smaller (patient enrollment occurred from 1998 to 2000). More availability of primary percutaneous coronary intervention during acute MI may alter the outcomes of similar patients in the future.

The REPLACE registry is the first prospective, multicenter study designed to collect complication data in patients for 6 months after replacement of a pacemaker, ICD, or CRT generator. Cohort 1 consisted of patients without (1,031) and cohort 2 of patients with (713) a planned

addition of a transvenous lead. The major complication rate was significantly higher in cohort 2 (15.3%) than in cohort 1 (4.0%). In both groups, major complications were higher among ICD than pacemaker replacements. Upgrading to or lead revision in CRT devices carried the highest major complication rate (18.7%). The 6-month infection rates were relatively low and similar in cohort 1 (1.4%) and cohort 2 (1.1%). However, a combined complication rate of 11.2% (4% for major and 7.2% for minor) over a 6-month period is unexpectedly high in procedures that were limited to generator replacements only. The combined rate jumped to 22.9% in concomitant lead revisions, with twice as many major than minor complications.

Remote Device Monitoring

Remote monitoring with full-interrogation of ICDs was first introduced in 2001 and extended to pacemakers in 2009. Wireless technology enables automatic device interrogation at scheduled intervals and transmission of data when triggered by alert events. Evidence for the benefit of remote monitoring was clearly demonstrated in 2 recent prospective randomized, multicenter trials. In the TRUST (Lumos-T Safely Reduces Routine Office Device Follow-up Trial), ICD patients with daily 24-h continuous wireless remote monitoring were compared to conventional in-office visits (47). Remote monitoring significantly reduced visits by 45% and enabled earlier detection of arrhythmic events without any increased in adverse events (death, stroke, and surgical intervention). In the CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision Trial), wireless remote monitoring of ICD patients significantly shortened event-to-clinical decision time and mean length of hospitalization compared to conventional device clinic visits, without adversely affecting mortality, hospitalization frequency, emergency department, or unscheduled clinic visits (48).

Translational Cardiac Electrophysiology

The long-QT syndromes are inherited diseases that are characterized by prolongation of the QT interval and risk of syncope and/or sudden death due to ventricular arrhythmias. To date, 12 genes have been identified and hundreds of mutations have been described (49). Most of the mutations involve loss of function of K^+ channels (particularly IKs and IKr) or gain of function of the Na^+ channels and, more rarely, involvement of Ca^{++} channels (50). Heretofore, channel function has been studied in heterologous systems (i.e., human embryonic kidney cells, and so forth) or mice or rabbit models. The relationship of these models to human cardiac cells has not been defined.

Recently, 3 studies have described the use of cardiac-induced pluripotential stem cells (IPSC) to simulate various forms of the long-QT syndrome. The first report came from Moretti et al. (51) who, in a landmark study, were able to generate functional myocytes from members of a family with a dominant missense mutation (R190Q) in the *KCNQ1* gene, which encodes for the Iks channel. Cells are prepared from the patients skin biopsy, and fibroblasts are induced to differentiate into pluripotential stem cells which are further coaxed to develop into cardiac myocytes (52,53). The authors were able to study both cell aggregates as well as individual cells from control subjects and the LQT1 patients. Microelectrode measurement of the respective action potentials showed that the LQT1 myocytes had a substantially longer action potential duration and a 75% to 80% reduction in the Iks current due to altered activation and deactivation of channel function. In addition, they showed that catecholamine-induced arrhythmias were attenuated with beta-blockers. This study confirms previous studies using heterologous systems and replicates well-known clinical observations (54).

The next report by Itzhaki et al. (55) described similar studies using fibroblasts from a patient with a missense mutation in the *KCNH2* gene (A614V), which encodes the Ikr channel. The authors found prolongation of the action potential duration in myocytes with the KCNH2 mutation compared to controls. Voltage clamp studies documented significant loss of Ikr current. Of interest was the finding of spontaneous early after depolarizations or even torsades de pointes recorded from surrogate extracellular electrocardiographic recording system (field potential duration). In a series of elegant studies, the authors exposed the control and affected myocytes with agents likely to enhance (K^+ channel-blockers E401 or cisapride) or ameliorate channel-blockade (i.e., KATP channel-openers, Ca^{++} channel-blockade and ranolazine, alate Na^+ channel-blocker). They found the expected results based on previous clinical experiments using heterologous systems. Of interest, ranolazine, while not affecting action potential duration still blocked induction of after depolarizations or arrhythmias. This remarkable study clearly demonstrates the power of this model to both replicate human disease processes and assess drug effects.

A third study (56) using similar methodology was applied to 2 patients with Timothy's syndrome. A single missense mutation involving the *CACNAIC* gene which encodes the α subunit of the L-type Ca^{++} channel results in a phenotype characterized by prolongation of the QT interval, syndactly, immune deficiency, and cognitive impairment (57). The genetic mutation responsible for Timothy's syndrome is associated with severe impairment of voltage-dependant inactivation of the channel, leading to a gain of function of the Ca^{++} current. The authors found that the affected myocytes had prolonged action potential duration, excess Ca^{++} influx, and irregular electrical activity on intracellular recordings. Of great interest was the finding that roscovitine, a compound known to increase voltage dependant inactivation of the L-type Ca^{++} channel, restored normal electrical function to the affected myocytes. These 3 studies as a group have shown beautiful replication of previous findings using heterologous systems and provide

for an exciting approach to study both mechanisms of arrhythmias and testing of new therapies.

Arrhythmogenic RV Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy is a cardiomyopathy that results in fibrofatty replacement of the RV wall. Important associated features are the frequent incidence of ventricular arrhythmias, particularly in athletes (57).

The molecular genetic basis of ARVC has been partially elucidated. It is known, for example, that approximately 50% of patients have been shown to harbor a mutation in the desmosomal genes. The desmosomes are responsible for cell to cell adhesion, and it is postulated that the sheer stress engendered by myocardial wall stress results in pulling apart of cells and replacement with fibrofatty tissue. Mutations in desmoplakin, plakoglobin, plakophilin 2, desmocillein 2, and desmoglein 2 have been identified in nearly 50% of affected patients. In addition, nondesmosomal genes (i.e., *TMEM43* and *TGFB3*) have also been identified (58).

The molecular pathogenesis of ARVC has been advanced by focusing on the effects of abnormal cellular localization of desmosomal plakoglobin. The latter results in reduction of canonical Wnt/β-catenin signaling transcription factors, which favors diversion of RV myocyte production into fatty and fibrous tissue (60,61). A recent review emphasizes the pathogenesis of ARVC on the basis of alternation in cardiac signaling pathways (58).

Another milestone paper focused on load-reducing therapy in progression of ARVC in a plakoglobin-deficient mouse model (61). The investigators studied littermates of heterozygous plakoglobin mice (plako +/−) and wild type control mice who underwent 7 weeks of intense daily swimming exercises. The mice were randomly allocated to receive load-reducing therapy consisting of nitrates and diuretics or no treatment. The treated group also received molsidomine to prevent nitrate tolerance. The authors showed load-reduction therapy resulted in prevention of RV dilation in the plako +/− mice. In addition, VT was more often initiated in the untreated group, and mapping studies suggested that the mechanism of VT was re-entrant. This is the first study to use animal models as a means to test therapeutic interventions for ARVC. Whether the concept or specific drugs used will be helpful in the clinical arena awaits further study. A thoughtful and provocative accompanying editorial by Calkins (62) is also worth reading.

Genetics and Molecular Biology of Pre-Excitation

Ventricular pre-excitation results from early activation of the ventricles by accessory AV nodal pathways. The pre-excitation pattern is usually associated with re-entrant arrhythmias and is known as the Wolff-Parkinson-White syndrome (WPW). To date, there are 3 known genes associated with WPW in humans. The first gene discovered was a mutation in the *PRAKG2* and subsequently in the *LAMP2* gene, which results in glycogen-storage myopathy (63–65). Mutations of BMP2 have been recently associated with WPW syndrome associated with cognitive dysfunction or Alagille syndrome (66,67). More recently, the importance of the notch signaling pathway in both development of the AV node as well as accessory pathways have been reported (68). It was found that notch inhibition disrupts AV nodal development, and invasive electrophysiologic studies showed a shorter A-H interval in notch-inhibited animals compared with controls. In contrast, gain of function of notch activity resulted in formation of an accessory pathway.

Aanhaanen et al. (69) described the effects of Tbx2-dependent changes in the development of the annulus. The investigators showed that inactivation of Tbx2 by another transcription factor (downstream to notch) required for formation of the annulus fibrosus leads to the formation of accessory pathways as well as malformation of the annulus. They nicely inscribed patterns of ventricular pre-excitation in these mice. They showed that affected mice expressed connexin-40, and connexin-43 as well as Na+ channels in the accessory pathways (all required for rapid conduction). The latter 2 articles add a great deal to our understanding of the normal development of the specialized conduction system as well as the annulus. In addition, the depiction of the accessory pathways are very similar to those described in humans, in contrast to those observed in mice with mutations in *PRAKG2* or *LAMP2*.

Reprint requests and correspondence: Dr. Gregory M. Marcus, University of California–San Francisco, 500 Parnassus Avenue, Box 1354, San Francisco, California 94143. E-mail: marcusg@medicine.ucsf.edu.

REFERENCES

1. Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010; 362:1363–73.
2. Van Gelder IC, Van Veldhuisen DJ, Crijns HJ, et al. Rate control efficacy in permanent atrial fibrillation: a comparison between lenient versus strict rate control in patients with and without heart failure. Background, aims, and design of RACE II. Am Heart J 2006;152: 420–6.
3. Kowey PR, Reiffel JA, Ellenbogen KA, Naccarelli GV, Pratt CM. Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomized controlled trial. JAMA 2010;304:2363–72.
4. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364:806–17.
5. Gaita F, Caponi D, Pianelli M, et al. Radiofrequency catheter ablation of atrial fibrillation: a cause of silent thromboembolism? Magnetic resonance imaging assessment of cerebral thromboembolism in patients undergoing ablation of atrial fibrillation. Circulation 2010;122: 1667–73.
6. Cappato R, Calkins H, Chen SA, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation 2005;111:1100–5.
7. Anfinsen OG, Gjesdal K, Brosstad F, et al. The activation of platelet function, coagulation, and fibrinolysis during radiofrequency catheter

ablation in heparinized patients. J Cardiovasc Electrophysiol 1999;10: 503–12.
8. Lee DS, Dorian P, Downar E, et al. Thrombogenicity of radiofrequency ablation procedures: what factors influence thrombin generation? Europace 2001;3:195–200.
9. Natale A, Raviele A, Arentz T, et al. Venice Chart International Consensus Document on atrial fibrillation ablation. J Cardiovasc Electrophysiol 2007;18:560–80.
10. Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Heart Rhythm 2007;4:816–61.
11. Di Biase L, Burkhardt JD, Mohanty P, et al. Periprocedural stroke and management of major bleeding complications in patients undergoing catheter ablation of atrial fibrillation: the impact of periprocedural therapeutic international normalized ratio. Circulation 2010;121: 2550–6.
12. Ouyang F, Tilz R, Chun J, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation 2010;122:2368–77.
13. Weerasooriya R, Khairy P, Litalien J, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol 2011;57:160–6.
14. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;57:223–42.
15. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360: 2066–78.
16. Marcus GM, Scheinman MM, Keung E. The year in clinical cardiac electrophysiology. J Am Coll Cardiol 2010;56:667–76.
17. Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360: 668–78.
18. Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358:2678–87.
19. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361: 1139–51.
20. Wann LS, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on Dabigatran): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;57:1330–7.
21. Weisfeldt ML, Everson-Stewart S, Sitlani C, et al. Ventricular tachyarrhythmias after cardiac arrest in public versus at home. N Engl J Med 2011;364:313–21.
22. Hallstrom AP, Ornato JP, Weisfeldt M, et al. Public-access defibrillation and survival after out-of-hospital cardiac arrest. N Engl J Med 2004;351:637–46.
23. Page RL, Joglar JA, Kowal RC, et al. Use of automated external defibrillators by a U.S. airline. N Engl J Med 2000;343:1210–6.
24. Valenzuela TD, Roe DJ, Nichol G, Clark LL, Spaite DW, Hardman RG. Outcomes of rapid defibrillation by security officers after cardiac arrest in casinos. N Engl J Med 2000;343:1206–9.
25. Bardy GH, Lee KL, Mark DB, et al. Home use of automated external defibrillators for sudden cardiac arrest. N Engl J Med 2008;358: 1793–804.
26. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA 2008; 300:1423–31.
27. Weisfeldt ML, Sitlani CM, Ornato JP, et al. Survival after application of automatic external defibrillators before arrival of the emergency medical system: evaluation in the resuscitation outcomes consortium population of 21 million. J Am Coll Cardiol 2010;55:1713–20.
28. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004;351:2481–8.
29. Steinbeck G, Andresen D, Seidl K, et al. Defibrillator implantation early after myocardial infarction. N Engl J Med 2009;361:1427–36.
30. Pouleur AC, Barkoudah E, Uno H, et al. Pathogenesis of sudden unexpected death in a clinical trial of patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. Circulation 2010;122:597–602.
31. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). J Am Coll Cardiol 2008;51:e1–62.
32. Tang, ASL, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363: 2385–95.
33. Moss AJ, Hall WJ, Cannom DS, et al., for the MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–38.
34. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011;123:1061–72.
35. Solomon SD, Foster E, Bourgoun M, et al. Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome. Multicenter Automatic Defibrillator Implantation Trial: Cardiac Resynchronization Therapy. Circulation 2010;122:985–92.
36. Arshad A, Moss AJ, Foster E, et al. Cardiac resynchronization therapy is more effective in women than in men. The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. J Am Coll Cardiol 2011;57:813–20.
37. Bilchick K, Kamath S, DiMarco JP, et al. Bundle-branch block morphology and other predictors of outcome after cardiac resynchronization therapy in Medicare patients. Circulation 2010; 122:2022–30.
38. Linde C, Abraham WT, Gold MR, Daubert C, for the REVERSE Study Group. Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients in relation to etiology: results from the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) study. J Am Coll Cardiol 2010 23;56:1826–31.
39. Cleao CJ, Shen W-K, Rea RF, et al. Differential outcome of cardiac resynchronization therapy in ischemic cardiomyopathy and idiopathic dilated cardiomyopathy. Heart Rhythm 2011;8:377–82.
40. Fornwalt BK, Sprague WW, BeDell P, et al. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. Circulation 2010:121:1985–91.
41. Kaszala K, Ellenbogen KA. When right may not be right. Right bundle-branch block and response to cardiac resynchronization therapy. Circulation 2010;122:1999–2001.
42. Sing JP, Klein HU, Huang DT, et al. Left ventricular lead position and clinical outcome in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CDT) trial. Circulation 2011;123:1159–66.
43. Goldbenbert I, Gillespie J, Moss AJ, et al. Long-term benefit of primary prevention with an implantable cardioverter defibrillator. An extended 8-year follow-up study of the Multicenter Automatic Defibrillator Implantation Trial II. Circulation 2010;122:1265–71.
44. Barsheshet A, Moss AJ, McNitt Scott, et al. Long-term implications of cumulative right ventricular pacing among patients with an implantable cardioverter-defibrillator. Heart Rhythm 2011;8:212–18.
45. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). J Am Coll Cardiol 2008;51:2085–105.
46. Dorian P, Hohnloser SH, Thorpe KE, et al. Mechanisms underlying the lack of effect of implantable cardioverter-defibrillator therapy on mortality in high-risk patients with recent myocardial infarction. Insights from the Defibrillation in Acute Myocardial Infarction Trial (DINAMIT). Circulation 2010;122:2645–52.
47. Varma, N, Epstein AE, Irimpen A, et al. Efficacy and safety of automatic remote monitoring for implantable cardioverter-defibrillator

follow-up. The Lumos-T Safely Reduces Routine Office Device Fellow-up (TRUST) trial. Circulation 2010;122:325–32.
48. Crossley GH, Boyle A, Vitense H, Chang Y, Mead RH, for the CONNECT Investigators. The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) trial: the value of wireless remote monitoring with automatic clinician alerts. J Am Coll Cardiol 2011;57:1181–9.
49. Roden DM. Long-QT syndrome. N Engl J Med 2008;358:169–176.
50. Hofmann F, Lacinová L, Klugbauer N. Voltage-dependent calcium channels: from structure to function. Rev Physiol Biochem Pharmacol 1999;139:33–87.
51. Moretti A, Bellin M, Welling A, et al. Patient-specific induced pluripotent stem-cell models for long-QT syndrome. N Engl J Med 2010;363:1397–409.
52. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007;131:861–72.
53. Zhang J, Wilson GF, Soerens AG, et al. Functional cardiomyocytes derived from human induced pluripotent stem cells. Circ Res 2009; 104:e30–41.
54. Moss AJ, Shimizu W, Wilde AA, et al. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. Circulation 2007;115: 2481–9.
55. Itzhaki I, Maizels L, Huber I, et al. Modelling the long QT syndrome with induced pluripotent stem cells. Nature 2011;471:225–9.
56. Yazawa M, Hsueh B, Jia X, et al. Using induced pluripotent stem cells to investigate cardiac phenotypes in Timothy syndrome. Nature 2011;471:230–4.
57. Splawski I, Timothy KW, Sharpe LM, et al. CaV1.2 Ca2+ channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell 2004;119:19–31.
58. Lombardi R, Marian AJ. Molecular genetics and pathogenesis of arrhythmogenic right ventricular cardiomyopathy: a disease of cardiac stem cells. Pediatr Cardiol 2011;32:360–5.
59. Garcia-Gras E, Lombardi R, Giocondo MJ, et al. Suppression of canonical Wnt/beta-catenin signaling by nuclear plakoglobin recapitulates phenotype of arrhythmogenic right ventricular cardiomyopathy. J Clin Invest 2006;116:2012–21.
60. Lombardi R, Dong J, Rodriguez G, et al. Genetic fate mapping identifies second heart field progenitor cells as a source of adipocytes in arrhythmogenic right ventricular cardiomyopathy. Circ Res 2009;104: 1076–84.
61. Fabritz L, Hoogendijk MG, Scicluna BP, et al. Load-reducing therapy prevents development of arrhythmogenic right ventricular cardiomyopathy in plakoglobin-deficient mice. J Am Coll Cardiol 2011;57: 740–50.
62. Calkins H. Use of mouse models to evaluate novel therapeutic approaches to treatment of arrhythmogenic right ventricular cardiomyopathy the future is now. J Am Coll Cardiol 2011;57:751–2.
63. Gollob MH, Green MS, Tang AS, et al. Identification of a gene responsible for familial Wolff-Parkinson-White syndrome. N Engl J Med 2001;344:1823–31.
64. Wolf CM, Arad M, Ahmad F, et al. Reversibility of PRKAG2 glycogen-storage cardiomyopathy and electrophysiological manifestations. Circulation 2008;117:144–54.
65. Yang Z, Funke BH, Cripe LH, et al. LAMP2 microdeletions in patients with Danon disease. Circ Cardiovasc Genet 2010;3:129–37.
66. Le Gloan L, Pichon O, Isidor B, et al. A 8.26Mb deletion in 6q16 and a 4.95Mb deletion in 20p12 including JAG1 and BMP2 in a patient with Alagille syndrome and Wolff-Parkinson-White syndrome. Eur J Med Genet 2008;51:651–7.
67. Lalani SR, Thakuria JV, Cox GF, et al. 20p12.3 microdeletion predisposes to Wolff-Parkinson-White syndrome with variable neurocognitive deficits. J Med Genet 2009;46:168–75.
68. Rentschler S, Harris BS, Kuznekoff L, et al. Notch signaling regulates murine atrioventricular conduction and the formation of accessory pathways. J Clin Invest 2011;121:525–33.
69. Aanhaanen WT, Boukens BJ, Sizarov A, et al. Defective Tbx2-dependent patterning of the atrioventricular canal myocardium causes accessory pathway formation in mice. J Clin Invest 2011;121:534–44.

Key Words: disorders ■ electrophysiology ■ rhythm.